Therapeutic Value of Radiofrequency Ablation of Hepatic Malignant Tumors

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Abstract

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Patients with primary and secondary malignancies of the liver are common. Liver is involved in 40% of adult patients who have primary tumors extrahepatic, and in cases with primary tumors, drained by the portal venous system (pancreas, large bowl, and stomach), liver is involved in as much as 75% of patients. Hepatocellular carcinoma (HCC) are the most common primary liver tumor, and metastatic liver tumours most often generate from colorectal carcinoma. Without treatment the median survival of HCC is 4 to 20 months and for CRM it is 5 to 13 months.

Surgical resection of hepatic tumours is the best treatment modality with potential for cure in selected patients. According to a recent report from March 2006, the overall survival after hepatic resection of colorectal metastases at 1, 5, and 10 years was 93%, 47%, and 28%, respectively. In fact, only 5% to 15% of newly diagnosed primary or secondary liver malignancies are amenable to surgical resection. Use of other methods which do not involve resection has been in focus and can be divided into systematic techniques such as chemotherapy and arterial infusion chemotherapy and direct ablation treatments such as cryotherapy, ethanol injection and thermal ablation by use of lasers, microwaves or radiofrequency. RFA involves the localized application of alternating current that creates a marked agitation of ions in the target tissue. Agitation results in frictional heat around the electrode and thermal coagulative necrosis.

The aim of the present study was to investigate the treatment efficacy of RFA and associated complications, based on available literature.

The included studies were heterogeneous and clear conclusions were difficult to draw. The best overall survival for RFA treatment according to the included studies was 93% for 1-year, 69% for 2-years, and 63% for 3-years. Major complications ranged from 0.9% to19.8% and minor from 4.7% to 32.5%.

At present the radiofrequency ablation seems to be a promising therapy, but these results are based on the uncontrolled non-randomised trials. Randomised trials are not available to support the use of this technique. After search in Cochrane database only one review was present and this too compared different treatment modalities for the treatment of HCC. Therefore conclusive evidence based on randomised trials for potential survival benefit from RFA of hepatic tumors is awaited.

INTRODUCTION

Primary and secondary malignancies of the liver are extremely common. The liver is second only to lymph nodes the most frequent site of metastasis from other solid cancers. Liver failure from extensive metastases often constitutes the main cause of death in patients with both colorectal cancer as well as a number of other common carcinomas.

Malignant hepatic tumours can be divided into primary and secondary metastases tumours. In many parts of the world primary liver cancer or hepatocellular carcinoma (HCC) is a common malignant tumour and represents a major public health problem. HCC accounts for 70-80% of all primary liver tumours and it is the sixth most common cancer in the world (fifth in men and ninth in women).The liver is also often the clinically predominant organ site of metastatic malignant disease. In secondary metastatic liver tumours colorectal carcinoma is most common. Colorectal is the 4th most common solid tumor world wide, after cancer of the lung, stomach, and liver [1 **discussion]**. It is 2nd most common cause of cancer death in the UK **[2 introduction]**. Colorectal metastases (CRM) of liver develop in 50% of the patients **[3 introduction]**. Most colorectal carcinoma deaths can be because of metastases and in many patients the liver is the only and initial site**.** About 10-25% of patients have liver metastases at the time of primary diagnosis and another 20-25% patients develop metachronous liver metastases **[4].** Without treatment the median survival of CRM is 5 to 13 months **[5].**

Surgical resection of primary and metastatic liver tumor is the optimal treatment modality with curative effect when disease is limited to the liver. 5-years survival after resection of HCC is given to be 25% to 30% **[6].** In a study 3, 4, and 5-years survival rate after hepatic resection of colorectal metastases has given to be 73%, 65%, and 58% respectively **[7].** Patients without extrahepatic disease and with good liver function and general condition are candidates for surgical resection. All liver metastases can be resected with at least 1 cm tumor free margin. Up to 75% of liver can be removed if the liver function is normal **[4].**

Several patients with hepatic malignancies are irresectable due to insufficient liver function (ex cirrhosis), extrahepatic disease or because of tumors location. Only 10% to 20% of patients are therefore candidates for surgical resection **[5],** and other interventional methods are needed. Methods that do not involve resection can be divided into systematic techniques such as chemotherapy , intravenous or arterial infusion, and into direct ablation treatments such as cryotherapy, ethanol injection and thermal ablation by use of lasers, microwaves or

radiofrequency. Radiofrequency ablation (RFA) has recently been developed for the focal treatment of inoperable liver tumours, and as a complementary technique to surgical resection when metastases are spread to both liver lobes.

The aim of the present study was to investigate the treatment efficacy of radiofrequency ablation (RFA), based on available literature, and to assess the value of this treatment modality, based on clinically relevant outcomes: Mortality, rate of recurrence, adverse events and quality of life.

Physical properties of RFA, different approaches and technical aspects;

Radiofrequency ablation has become a widely used ablative technique for hepatic tumors. RFA involves the localized application of thermal energy to destroy tumor cells. In monopolar RF ablation, the patient is part of a closed loop circuit that includes a RF generator, an electrode needle and ground pads. An alternating electric field is created within the tissue of the patient. The liver tissue has relatively high electrical resistance in comparison with the metal electrode. The tissue ions attempt to follow the changes in direction of alternating electric current. This creates a marked agitation of the ions present in the target tissue that surrounds the electrode. The agitation results in frictional heat around the electrode and thermal coagulative necrosis. The discripency between the small surface area of the needle electrode and the large area of the ground pads causes the generated heat to be focused and concentrated around the needle electrode **[8, 9, 10, 11].**

The thermal damage caused by thermal heating depends on both the tissue temperature achieved and the duration of the heating of the tissue. Heating of tissue at 50-55°C for 4-6 minutes produces irreversible damage to cells. At temperatures between 60°C and 100°C, immediate coagulation of tissue is induced, with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At 110°C , tissue vaporizes and carbonizes. To get complete destruction of tumor tissue, the entire tumor volume must be heated to cytotoxic temperatures. RF induced necrosis is different from ordinary tissue death. In heat ablation the effected structures are subjected to thermal fixation. With staining techniques the tissue structure is preserved with absence of enzymatic activity. Modern radiofrequency system has a temperature sensor at the tip of the electrode to note the temperature. With temperatures higher than 110°C the tissue around the probe act as an electrical isolator, which further stops the passage of current and therefore decrease the effectiveness of ablation. With a cooled-needle electrode, it is possible to enlarge the area destroyed by radiofrequency ablation

compared with that achieved with a bare electrode. This cooling process reduces the heat accumulation close to the needle and therefore allows diffusion of the current away from the needle. Treatment efficacy after ablation can be controlled by contrast enhanced CT or MR. Complete ablation is demonstrated by the absence of enhancement. Immediately after ablation it can see gas within the ablation zone with small amount of haemorrhage and reactive hyperaemia around the tumor. Despite the appearance of complete ablation, recurrence adjacent the ablated area can occur particularly where blood flow in adjacent vessels results in tissue cooling **[8, 9, 10, 11, 12].**

RF can be performed using image guidance with percutaneous, laparoscopic approaches or at open laparotomy. At open laparotomy RF can be combined with liver resection, that is resection of one area of liver and ablation of the other. Open approach permits accurate RFA treatment for tumors near the inferior vena cava or the hepatic veins and to combine temporary hepatic vascular inflow occlusion called Pringle maneuver. Tissue perfusion has a direct impact on the volume of necrosis that can be produced. Inflow occlusion increases the size of the zone of necrosis by reducing intramural and peritumoral blood flow with a resultant decrease in flow related cooling of tissue but it also removes the protective effect of blood flow and as a result there is also increase risk of bile duct injury **[12, 13].**
RFA has been used as a treatment for osteoid osteoma, HCC, renal cell carcinoma, hyper functioning parathyroid adenoma. It has also been used to destroy lesions of the lung, kidney, bone, adrenal glands, spleen, breast, lymph nodes, pelvis, prostate, neural tissue, and liver **[6, 12 introduction, 14].**

There has been technical development in the treatment of RFA. The two main strategies that have been developed to increase the amount of ablated tumor parenchyma are use of several array needles or probe needles with radiofrequency energy applied through each array or probe and electrode cooling. Comparison of water cooled system with expandable array systems showed that the cooled tip needle induced larger lesions as a result of thermal ablation compared with the expandable multi array, but ablation with the expandable system was more uniform and sphere **[9].**

METHODS

The literature search was mainly conducted using database PubMed. The main period for research was November/December 2004. Search was also made in January/February 2006 but to a lesser extent. Words used to search the literature relevant to the question that is to be answered was hepatic or liver tumor, Radiofrequency ablation, Thermal radiofrequency ablation, Percutaneous / laparoscopic / open radiofrequency ablation, combined resection and RFA, complications of radiofrequency ablation and tumor malignancies.

Relevant articles from the reference list of the studies were also searched. Some articles are also from periodicals. Books on the topic of hepathology with clinical aspects and books on surgery were used from the library. The systematic review articles on complications and radiofrequency ablation are also included in this literature from the search from database.

I tried to choose studies that include both primary and secondary liver tumors. Hence hepatocellular carcinoma and colorectal metastases (CRM) are the most frequent tumors in both categories some articles only concentrate on CRM and these studies are also included here. In other articles patients with tumor both from HCC and other sites are present.

During the search in world literature, I found and overview, published in September 2003 from the UK National Institute for Clinical Excellence **[15]**, performed for the UK Procedures Advisory Committee. Until 2003 there was not published any randomised controlled trial (RTC), comparing the clinical outcome after RFA and surgery, treating primary or secondary liver malignancies.

I therefore searced in the Cochrane Library for any RTC comparing RFA with any other treatment modality, and found one Cochrane report **[16]**, referring two randomised trials, both comparing RFA with percutaneous ethanol injection **[17]** and microwave coagulation therapy respectively **[18].**

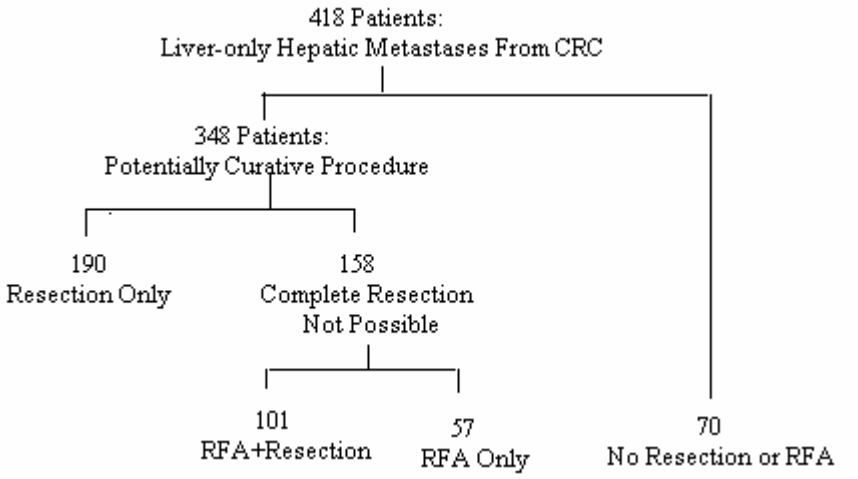
As there is still no published RTC comparing RFA with surgery, I selected publications with the best prospective data I could find, and focused on the six selected papers among others.

RESULTS

The aim of this study is to evaluate RFA efficacy and safety. It is important to have randomized control trials to answer this question. Adequate generation of the allocation, blinding and follow up of interventional and control group is the only way to have two groups that can be compared for outcomes. After search in the Cochrane database as mentioned above, there was only one review study on RFA **[16]**, but in this review the radiofrequency was compared with two other treatment modalities for hepatic tumours. In this part I will present the results from six articles out of nearly 26, also including reviews and complications related to procedure. None of these studies are randomized trials. One study of Abdalla et al **[7]**, is a retrospective study whereas the other five are prospective uncontrolled observative studies. Among these six studies, two studies use percutaneous, one laparoscopic and one use all three approaches for RFA. One study used combined resection and RFA. Another one compared only resection, resection+RFA, only RFA and only chemotherapy as treatment modalities. Two studies included only patients with colorectal metastases, and four studies had patients with mix tumor type.

Abdalla et al. [7]

The aim of the study was to examine recurrence and survival rates for patients treated with hepatic resection only, RFA plus resection and RFA only for colorectal liver metastases. They performed a retrospective analysis of patients operated for colorectal metastases confined to the liver. 418 patients were included in the study. All patients were treated between 1992 and 2002. Patients were divided into two groups. Group 1, included 348 who were treated for cure with hepatic resection only, RFA+resection and RFA only. RFA alone or in combination was confined to the patients who were considered to be unresectable and in whom complete resection could not leave sufficient vascularized hepatic parenchyma to support post resection hepatic function. In the second group there were 70 patients and based on preoperative and intraoperativ findings were considered not to undergo curative therapy because of disease distribution or extent (but no extra hepatic disease) and too extensiveness of disease. These patients underwent chemotherapy (systemic, intra-arterial or intra-arterial +systemic chemotherapy). Of 348 patients from first group 190 underwent resection only, 101 RFA+resection and 57 RFA only.



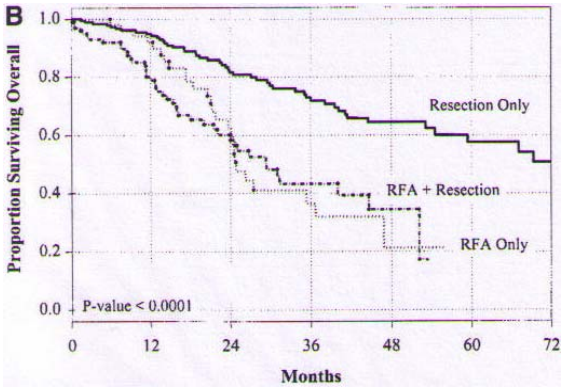
Preoperative chest radiograph or CT when indicated and abdominopelvic CT or MR was done in all patients. No patient underwent prior hepatic resection or RFA. Selection criterion for surgical treatment was complete tumor resection or RFA with preservation of sufficient hepatic parenchyma. RFA was not performed adjacent to major biliary structures. Patients with tumor close to major hepatic vein branch or major biliary structures were considered for RFA. All patients underwent open laparotomy. No patients were treated percutaeously. Itraoperative ultrasonograghy was used in RFA treatment to localize tumor.

Tumor Recurrence:

In 57 patients who underwent RFA only, a total of 110 tumors were ablated. The number of tumors treated per patient was ranged from 1 to 8. Median tumor size was 2,5 cm. Recurrence of any kind occurred most often after RFA only. Recurrence in RFA only was 84%, in RFA+resection 63% and in resection only 52%. The dominant pattern was intrahepatic recurrence. Recurrence anywhere in the liver (without extra hepatic) was fourfold more frequent after RFA only than resection only (44% vs. 11%). Whereas it was double after RFA+resection than resection only (28% vs. 11%).

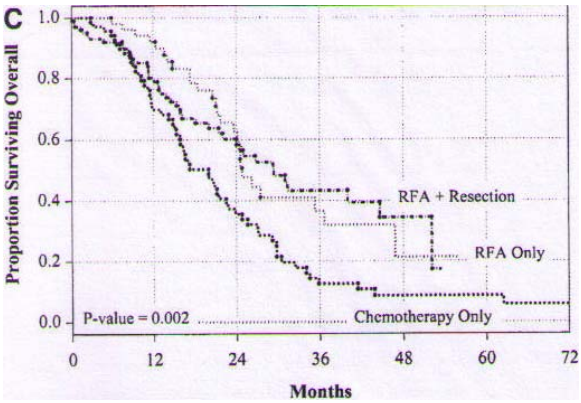
Overall Survival:

Median follow up time for first group, 348 patients, treated for cure was 21 months. Best survival rate was in patients who underwent resection only with 3-years survival 73%, 4-year 65% and 5-year 58%. There was no significant difference in survival between groups treated with RFA+resection and those who were treated with RFA only. 3-years survival was 43% in RFA+resection vs. 37% in RFA only. 4-year survival was 36% vs. 22%.



Survival stratified by surgical treatment of cure

Statistically significant difference was found in survival for those who were treated with RFA as a component of therapy and in those with chemotherapy.



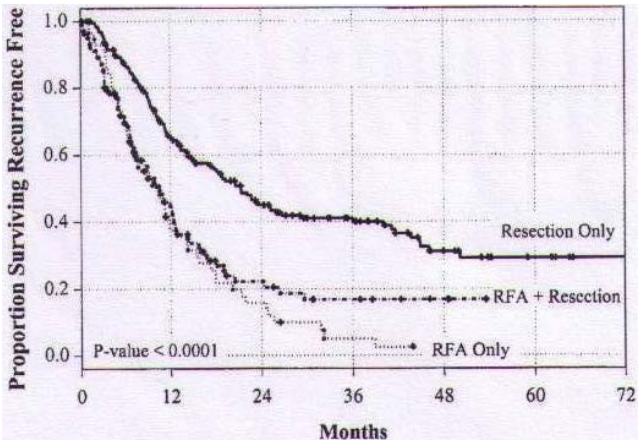
Survival stratified by treatment of "unresectable" patients

Overall survival was best for patients treated with solitary tumors, intermediate for 2 to 3 tumors and worst for >3 tumors.

Treatment of a solitary tumor by resection only provided survival better than treatment of a solitary tumor by RFA only.

Recurrence Free Survival:

It was best recurrence free survival for patients treated with resection only. There was no significant difference in recurrence free survival for patients treated with RFA+resection and those with RFA only.



Recurrence free survival

Conclusion;

Hepatic resection is the treatment of choice for colorectal liver metastases. RFA alone or in combination with resection for unresectable patients does not provide survival comparable to resection, and provides survival only slightly superior to non surgical treatment.

Solbiati et al; [14]

The aim of the study was to describe the results of RFA in patients with hepatic metastases from colorectal carcinoma.The study included 117 patients with 179 metachronus colorectal liver metastases. They were treated with percutaneous RF ablation from July 1995 to October 1999. Mean age of patients was 64.8 years. Mean diameter of tumors was 2.8 cm. (range, 0.6-9.6 cm.). All metastases were at least 1 cm from the hepatic helium, gallbladder or bowl wall. All patients had undergone primary tumor resection prior to ablation. Malignancy of at least one tumor was obtained by ultrasonography guided aspiration biopsy. Patients could not undergo resection due to extra hepatic metastases, prior metastastectomy, age disease extent and co morbidity. 17% patients get systemic chemotherapy only before ablation, 72% before and after and 11% did not get any chemotherapy.

All patients were examined by CT and biopsy before treatment. Cool –tip single or cluster electrodes were used under guidance of US. Mean procedure time was 45 minutes per session including tumor localization, treatment, and electrode removal and post procedure US. Follow up CT was performed 7-14 days after ablation. Areas that did not enhance with contrast were considered to be necrotic tissue. It was determined the effect of number of metastases on the time to new metastases and to death and the effect of tumor size on local recurrence.

Results;

A total of 229 RF ablations were performed in 117 patients with 179 tumors. Technical success was achieved in 98% (176) of tumors. Follow up ranged from 6 to 52 months. Mortality rate was 31% (36 patients). The time until death was not significantly related to the

number of metastases or the size of largest lesions. The mean time to death appears to decrease as the number of metastases or the diameter increases.

TABLE. Time to Death by Number of Metastases

No. of Metastases	No. of Deaths/ No. of Patients	Estimated Median (mo)	Estimated Mean* (mo)
1	28/74 (37.8)	33	34.5
2	5/29 (17.2)	NA	20.1
3	3/9 (33.3)	25	21.7
4	0/5 (0.0)	NA	NA
All	36/117 (30.8)	36†	35.4†

Note.—NA = not available; median was not estimable in group due to the small number of occurrences among the cases in the group and/or to censoring of the longest times observed. Numbers in parentheses are percentages

TABLE. Time to Death by Diameter of Largest Metastasis

Maximum Diameter (cm)	No. of Deaths/ No. of Patients	Estimated Median (mo)	Estimated Mean* (mo)
≤2.5	14/37 (37.8)	42	33.1
2.6–4.0	14/61 (21.9)	NA	30.7
≥4.1	8/19 (42.1)	22	22.7
All	36/117 (30.8)	36	35.4†

Note.—NA = not available; median was not estimable in group due to both the small number of occurrences among the cases in the group and to the censoring of the longest times observed. Numbers in parentheses are percentages. * Possibly biased. †Mean and median for all patients are greater than respective estimates in all four subgroups, which reflects the distortions of censoring.

Median survival for all patients was 36 months. 1, 2 and 3 years survival was 93%, 69% and 46% respectively. 57% (67 patients) had new metastases. Median time of new metastases was 12 months. The patients with no new metastases (tumor free suival) at 1 and 2 years after ablation were 49% and 35% respectively. Time to new metastases was not significantly related to number of metastases.

TABLE 3. Time to New Metastases

No. of Metastases	No. with New Metastases/ No. of Patients	Estimated Median (mo)	Estimated Mean* (mo)
1	44/74 (59.5)	12	15.5
2	15/29 (51.7)	18	17.3
3	4/9 (44.4)	NA	8.1
4	4/5 (80.0)	3	5.4
All	67/117 (57.3)	12	16.1

Note.—NA = not available; median was not estimable in group due to both the small number of occurrences among the cases in the group and to the censoring of the longest times observed. Numbers in parentheses are percentages. * Possibly biased.

70 lesions (39.1% lesions) of the 179 had local recurrence observed after treatment. Local recurrence rate at 18 months was 44%. No local recurrence was observed after 18 months. The lesions with no local recurrence at 6 months and 1 year were 69% and 60% respectively. Time to local recurrence decreased with increasing lesion size, while frequency of recurrence increased. Among those with local recurrence, retreatment does not appear to alter the like hood of survival. However there was a trend toward longer survival in patients with retreatment.

Complications;

Following complications were observed;

- One case of perforation of right colon adjacent to an exophytic metastasis. Patient develop sign of perforation 2 days after ablation and underwent laparotomy.
- Abdominal pain in one patient 3-4 hours post procedure. Tumor was treated at the dom of the liver. Patient had orthostatic hypotension and intraperitoneal hemorrhage was as noted on CT scan.

Conclusion;

RF ablation is an effective method to treat hepatic metastases from colorectal carcinoma.

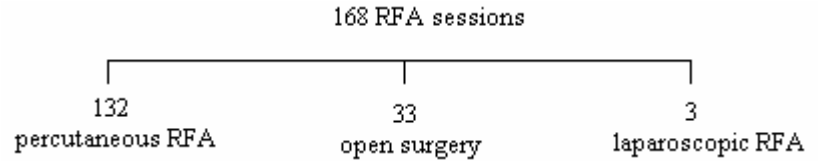
Lannitti et al: [6]

The objective of the study was to observe the efficacy of hepatic radiofrequency ablation in the treatment of unresectable hepatic malignancies.

123 patients with hepatic malignancies were treated with percutaneous, laparoscopic and open RFA from January 1998 through September 2001. Patients had histological documented hepatic malignancies. They were treated with RAF if it was unresectable tumors, not

sufficient liver function, medical condition that inhibited abdominal surgery and tumors that could not be treated by resection. Percutaneous RF was performed under conscious sedation, surgical RFA under general anaesthesia and with intraoperative US. For laparoscopic procedure US was also used. An internally cooled clustered RF electrode was used for all ablations. In patients with 4 or more lesions, operative RFA was used.

Average age of patients was 65 years. Of 123 patients, 52 patients had metastasis colorectal cancer, 30 hepatocellular carcinoma. 41 patients had other histological findings including hepatoblastoma, sarcoma, intrahepatic cholangiocarcinoma and metastases from other sites (renal, breast, melanoma, oesophagus, lung, gastric, gallbladder, carcinoid, thyroid and neuroendocrine tumors). It was performed a total of 168 RFA sessions. Of 168, 132 were treated with percutaneous, 33 with open surgery and 3 with laparoscopic RFA. Due recurrence and incomplete ablation several patients had ablation several times. For all ablations cooled clustered RF electrode was used. Post procedural systemic chemotherapy was offered to patients on the basis of their performance status and the histological features of their disease.



Results and complications;

Median follow up time was 20 months (range, 1-47 months). Median tumor size was 5.2 cm (range, 0.5-15.0 cm). Follow up for all patients included imaging every 3 to 6 months. 0verall survival for patients with metastatic colorectal cancer at 1 year was 87%, at 2 years 77% and at 3 years 50%. For patients with hepatocellular carcinoma overall survival was 92% at 1 year, 75% at 2 years and 60% at 3 years.

- Mortality rate was 0.6% (of total RFA sessions) due to cerebrovascular accident.
- Total morbidity rate was 7.1% for 168 ablation sessions. The most commonly encountered patient complaints are focal discomfort at the probe entry site and flu like symptoms known as post ablation syndrome.
- Hepatic abscesses occurred in 4 patients. Each patient had significant risk factors such as advances cirrhosis, underlying chronic cholangitis and previous left sided colectomy during the same operation as RFA.

Hepatic Radiofrequency Ablation Morbidity and Mortality*

	No. (%) of Ablation Sessions (N = 168)
30-Day mortality (CVA)	1 (0.6)
Morbidity	
Hepatic abscess	4 (2.4)
Liver dysfunction	3 (1.8)
Segmental infarcts	2 (1.2)
Vascular fistula	1 (0.6)
Diaphragm paralysis	1 (0.6)
Systemic hemolysis	1 (0.6)
Total	**12** (7.1)

Conclusions;

Hepatic RFA is an effective treatment option for patients with unresectable hepatic tumors. Careful patient selection based on tumor size, location and number and on patients clinical status should determine the choice of treatment. Further controlled trials are needed to determine the effect of hepatic RFA on long term survival.

T. M Pawlik et al: [11]

The objective of the study was to examine the safety and efficacy of hepatic resection combined with RFA.

172 patients were included in the study and all underwent combined hepatic resection with intraoperative RFA. Inclusions criteria were histologically confirmed primary or metastatic hepatic malignancies with no extra hepatic disease. To be eligible, patients had to have multifocal hepatic disease that was unresectable due to location of tumor or volume of the liver involved. Patients were surgically unresectable for cure because of number or bilobar loction of the tumor, tumor location to major vascular structures, and the presence of cirrhosis hepatic reserve not sufficient to tolerate major hepatic resection. Patients were considered candidates for RFA even if the tumor was localized near major hepatic or portal vein or vena cava inferior, but they were excluded if tumor involved bile ducts because thermal heat from RFA could destroy major bile ducts.

Serum laboratory tests were taken of all patients and they were evaluated with baseline history. CT or MR scan of the abdomen and pelvis, and the chest radiograph was taken. Patients were excluded if they had less platelet count or if prothrombin time was prolonged. Those patients with less white blood count or a bilirubin>2.0 mg/dl were also excluded.

All patients were treated surgically with both RFA and resection in one operation. Initial exploration was performed on entering the abdomen to see if extrahepatic disease was

present. An intraoperative ultrasound was also used to localize the tumor and find its proximity to vessels. After treatment same serum blood tests were obtained on days 1, 7 and 30 that was taken before procedure. It was also performed CT or MR of chest and abdomen postoperatively at different time interval. Recurrence was detected by CT/MR or via biopsy diagnosis.

Results;

172 patients were treated using both resection and RFA. Median age was 56.2 years. Majority of the patients had metastases from colorectal cancer. Other tumor forms are shown in table.

TABLE 1. *Characteristics of the 172 patients treated with hepatic resection and RFA*

		n (%)
Median age (y)	56.2 (range, 12–86)	
Gender		
Female		70 (40.1)
Male		102 (59.9)
Histology of hepatic disease		
Colorectal metastasis		124 (72.1)
Leiomyosarcoma metastasis		13 (7.6)
Carcinoid metastasis		10 (5.8)
Hepatocellular carcinoma		5 (2.9)
Pancreas metastasis		4 (2.4)
Neuroendocrine metastasis		3 (1.7)
Breast metastasis		4 (2.4)
Sarcoma metastasis NOS		3 (1.7)
Cholangiocarcinoma		2 (1.1)
Ocular melanoma metastasis		1 (.6)
Other		3 (1.7)

RFA, radiofrequency ablation; NOS, not otherwise specified.

Patients with noncolorectal tumors had lesions restricted to liver and was responding to or was stable on systemic chemotherapy. A total of 737 tumors were treated, 350 with RFA and 387 with resection. The median number of tumor per patient was 3 (range, 2-21). The median number of tumor surgically treated per patient was 2 (range1-9) and those with ablation was 1 (range, 1-12). Median operative time for the combine procedure was 3.0 hours (range, 1- 8.13 hours). After removal of the index lesion or lesions, the remaining unresectable lesions were treated with RFA following a standardized treatment. Combing RFA with resection was generally well tolerated with minimal complexity or morbidity to the operation. The median operative time for combined procedure was 3.0 hours (range 1-8.13 hours) with a median blood loss of 200cc.

Complications;

RFA associated complication was one partial thickness thermal injury to stomach. Postoperative complication rate was 19.8% including 2.3% mortality rate. A number of complications were minor and not necessarily related to procedure. Prolonged postoperative

ileus, urinary tract infections, and pleural effusion were not necessarily related with procedure. Intermediate complications included tachycardia, biloma, perihepatic abscess and pneumonia.There was no relation between resection extent and number of tumors ablated with postoperative complications. Adult respiratory distress syndrome, multisystem organ/hepatic failure, postoperative bleeding and pulmonary embolus were uncommon major complications and occurred in the patients who died postoperatively. 2 of the deaths among 4 were related to liver failure and one death was due to postoperative bleeding and cardiac arrest.

	n (%)
Ascites	1 (.6)
Adult respiratory distress syndrome	1 (.6)
Cardiac event	3 (1.7)
Fluid collection/biloma	4 (2.3)
Multisystem organ failure/hepatic failure	3 (1.7)
Perihepatic abscess	3 (1.7)
Pleural effusion	1 (.6)
Pneumonia	5 (2.9)
Pneumothorax	1 (.6)
Postoperative bleed	1 (.6)
Postoperative death	4 (2.3)
Prolonged postoperative ileus	4 (2.3)
Pulmonary embolus	1 (.6)
Thermal injury to stomach	1 (.6)
Urinary tract infection	1 (.6)
Total complication rate:	19.8%

Postoperative complications and deaths

Recurrence:

Median follow up time was 21,3 months with tumor recurrence rate 56,9% (98 patients). The site of first recurrence was isolated to the RFA site in 8 patients (8,2%), a non-RFA hepatic recurrence in 38 patients (38,8%), a non-RFA hepatic recurrence plus distant disease in 31 patients (31.6%) and isolated distant disease in 21 patients (21.4%). The median time to failure was about 7,5 months in all patients. Most frequent distant disease was pulmonary metastases. RFA recurrence in patients was 8,2% that means 8 out of 172 recurred, but there were only 8 treatment site failure out of 350 tumors treated with RFA (2.3%).

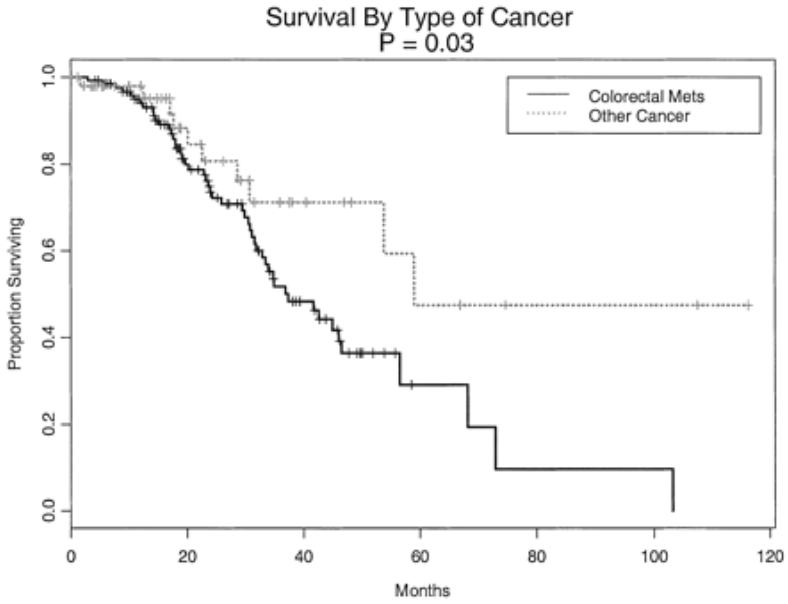
Site of first recurrence	No. of patients (n = 98) n (%)	Median time to failure (mo)	Range (mo)
RFA site	8 (8.2)	7.5	(1.5–19.1)
Non-RFA hepatic recurrence	38 (38.8)	7.5	(1.0–29.7)
Non-RFA hepatic recurrence plus distant disease	31 (31.6)	7.5	(2.3–23.4)
Distant disease only	21 (21.4)	7.6	(3.2–26.5)

Details of tumor recurrence after hepatic resection and RFA: overall recurrence rate

The only factor that affected time to recurrence was the total number of tumors treated.There was statistically significant difference in time to recurrence in those patients who had more than 10 tumors treated (tumors treated combined with resection and ablation). Patients more than 10 tumor had shorter median disease free survival time of 2,3 months as compared to those who had fewer tumors than 10, that is 7,6 – 10,3 months. Median time to recurrence was not effected by the number and size of tumor treated with RFA. In all cases median time to recurrence was <12 months.

Survival:

Overall survival time was 45,5 months. In the follow up time mortality rate was 34,8% (60 patients), and 65,2% (112 patients) were still alive. Significant factors affecting overall survival were type of tumor and amount of blood loss. Patients with noncolorectal metastases had a median survival time of 59 months that was better than colorectal metastases with median survival time of 37.3 months. The amount of surgical blood loss also significantly affects overall survival.



Surgical blood loss had significant affect on survival. Those with >1000 cc blood loss had a median survival time of 30.5 months. Patients with <250 cc blood loss had median survival of 42.6 months and <250-1000 had 56.6 months. Other factors such as age, number of RFA tumors, type of surgery and total number of tumors treated did not significantly affect survival on univariate analysis. Patients with synchronous colorectal metastases had a better overall survival as compared to patients with metachronous metastases. Size of RFA tumor was the only factor that significantly affected survival. Lesion > 3 cm had a higher like hood of death than those with lesion ≤3 cm.

Conclusion;

Resection combined with RFA provides a surgical option to patients who are unresectable, and this may increase long term survival.

Chung M. H. et al; [19]

The purpose of the study was to analyse efficacy of laparoscopic interoperate ultrasound and laparoscopic RFA in patients with unresectable hepatic tumors.

Patients unresecable for primary or metastatic tumors without extra hepatic disease were included in the study. Patients were unresecable if they had tumors number greater than 4, bilobar disease and localization of tumor near major vascular and biliary vessels. Patients in the study were at least 18 years old with a life expectancy of at least 4 months. Pregnancy, active infection and chemotherapy/ biotherapy/radiotherapy were exclusions criteria. Patients who could not undergo laparoscopy or laparotomy, those with tumors occupying more than 40% of the liver and those who had received hepatic arterial infusion pump were also excluded from study.

Study included 27 patients and all these underwent complete history and physical examination, serum tests, chest radiography and other imaging. Laparoscopy was used to examine any extra hepatic tumor and all eight liver segments. 15 gauge needle RFA was used. In second year of study larger lesions were ablated using a cool tipped probe electrode. Probe tract was cauterized as the RF needle was withdrawn after completion of the ablation.

All patients underwent laparoscopic RFA. Among the 27 patients 25 had received adjuvant therapy and 11 had undergone abdominal surgery. Mean age of patient was 59 years. Total number of ablated tumor was 85. Tumor type was hepatocellular carcinoma and metastases from colon, breast cancer, carcinoid, lung adenocarcinom, sarcoma, tongue and melanoma.

Tumor type	**NO. of paients**	**No. of tumors**
Melanoma	8	31
Colon adenocarcinoma	6	14
Breast carcinoma	3	7
Hepatocelluar carcinoma	4	10
Carcinoid	3	14
Lung adenocarcinoma	1	3
Srcoma (leiomyosarcoma)	1	4
Tongue (adenoid cyst)	1	2
Total	*27*	*85*

Results;

85 malignant tumors were ablated. The mean diameter of tumor was 2.6cm (range, 1.3- 5cm). Most of the patients had multiple tumors with mean 3.1 tumors (range, 1-8 tumors). Of the 27 patients 14(52%) had bilobar hepatic tumor, 7(26%) had centrally located tumor and 6(22%) had tumor confined to the right lobe of the liver. No patient was found to have extra hepatic tumor by laparoscopic examine. However by laparoscopic intraoperativ ultrasound it was found that 10 (37%) had additional hepatic lesions which were not identified preoperative imaging. these lesions were for the most small in size, <1cm, located on the surface or near the surface of liver. These additional tumors were also treated by RFA. Mean follow up time was 14 months (range, 2-27 months). Mean hospital stay for all patients was 1.3 days (range, 1-7 days).

Mean survival was 10 months (range, 2- 18 months). 11 (41%) patients were disease-free. At the end of the study 6 (22%) were alive with disease and 10 (37%) have died with disease. Local recurrence rate in patients was 4 (15%) and local tumor recurrence was 4 (4.7%). local recurrence occurred in one patient with hepatocellular carcinoma. The other three patients had metastatic melanoma.

Complications;

There was only one postoperative complication. It was postoperative bleeding in one (4%) patient because of underlying thrombocytopenia. No treatment related mortality was seen.

Conclusion;

Laparoscopic RFA and intraoperativ ultrasound constitute a safe and accurate method for ablation of unresectable hepatic tumors.

Chen MH et al; [20]

The aim of the study was to investigate the treatment efficacy of radiofrequency ablation (RFA) of hepatic malignant tumors and the relevant complications.

338 patients with 763 hepatic tumors underwent 565 ultrasound guided percutaneous RFA from 1999 to 2004. All patients were diagnosed by biopsy at least on one lesion. Mean age for men was 59.1 years and for women it was 58.6 years. 204 patients had hepatic cellular carcinoma (HCC) with 430 tumors with mean diameter of 4.0 cm (range 1.2-10.8 cm). Of 204 patients with HCC 48 were in stage I-II and 156 patients were in stages III-IV according to UICC-NTM staging system. Of total 338 patients, 134 patients had metastatic liver

carcinomas (MLC) with 333 lesions with a mean diameter of 4.1 cm (range 1-10.0 c.m). 11 patients had extrahepatic metastases when the first RFA was performed.

Primary tumor site of MLC	**Number of patients**
Gastric and colorectal tract	96 (71.6%)
Breast cancer	16
Lung cancer	10
Pancreatic cancer	5
Other organs	7
Total patients	*134*

61.8% patients (209/338) had tumors larger than 3.5 cm. 51 patients had 54 tumors adjacent to gastrointestinal tract and 46 patients with 51 tumors adjacent to gallbladder in this group. The RF system used was 460 kHz generator and the electrode contained nine hook-shapes prongs that could deployed from the canula. 93% of the patients were treated using established protocol. The treatmet protocol was decided according to the ablation range. Ultrasound was used to monitor the electrode placement. All patients underwent percutaneous RFA under general anesthesia. For irregular tumors larger than 5 cm and near gastrointestinal tract CT within 24 h after the treatment was used to detect any residual viable tissue and to observe possible complications. 1 month after ablation contrast enhanced CT was performed to evaluate tumor respons to therapy. Complete ablation was considered to achieve if ablation zone was beyond tumor border, margin of ablation was clear and smooth and no contrast was detected within or near tumor. The patients were follow up later by serum α-fetoprotein (AFP), abdominal US and CT. Follow up period was 3-57 months.

Results;

The ablation success rate of initial RFA was 94,8% (723/763 tumors).Complete ablation success after the first RFA based on the CT findings was 93.3% (401/430 tumors) for HCC and for MLC was 96.7% (322/333 tumors). Overall residual rate was 11.2% (38/338 patients) of which 31 cases (81.6%) had tumor larger than 3.5 cm. Success rate for tumor larger than 3.5 cm was 85.2% (178/209 patients).

Tumor type	No. of patients	No. of tumors	Mean tumor size	No.of tumors completely ablated (%)	No. of local recurrence (%)
HCC	204	430	4.0	401 (93.3)	34 (7.9)
MLC	134	333	4.1	322 (96.7)	35 (10.5)
Total	338	763	4.1	723 (94.8)	69 (9.0)

For tumors adjacent to bowel ablation success rate was 83.3% (45/54 tumors) it was 86.3% (44/51 tumors) for tumor adjacent to gallbladder. Local tumor recurrence was found in 34 of HCC patients (7.9%) and 35 of MLC patients (10.5%) after follow up of 3-57 months. 40.5% of patients received additional 2-11 RFA treatments because of metastases or recurrence. The overall survival rate of 300 patients with malignant liver tumor after RFA was 80.6%, 60.1% and 50.4% for 1st, 2nd and 3rd year respectively. The survival rate for metastatic tumor for 1, 2 and 3-year was 75.3%, 50.2% and 25.1% respectively. HCC patients survival after 1, 2, 3-year was 84.6%, 66.6% and 63.1%. The overall survival rate was higher in HCC group than in MLC.

Complications;

Major complications occoured in 2.5% procedures (14/565). Minor complications consisted of bellyache, shoulder pain, breath-related ight superior bellyache, fever and transient hepatic dysfunction.

Major complications	**Number of patients**
hemorrhage	5
bile leakage	2
colon perforation	1
stricture of bile duct	2
cholecystitis	1
hemothorax	2
Skin burn	1

Conclusion;

RFA is minimally invasive local treatment and has become an effective and safe alternative for patients of hepatic malignant tumor, even of advanced liver tumor, tumor recurrence, and liver metastases.

Complications of RFA;

RFA has proven to be safe and efficacy method to treat the malign tumors of liver. It has received increasing attention as a promising technique. There are some complications that are attended with treatment procedure. Early detection and proper management of complications are possible only if the physician performing RF ablation understands the broad spectrum of complications. This can minimize the complications and help to exclude high risk patients. Complications can be of those related to imaging guided electrode placement, such as bleeding, infection, tumor seeding, and pneumothorax and those that are related to thermal therapy. Complications related to thermal therapy can damage organs adjacent to ablated tumor and grounding pad burns **[21].**

Bleeding; **[21, 22]**

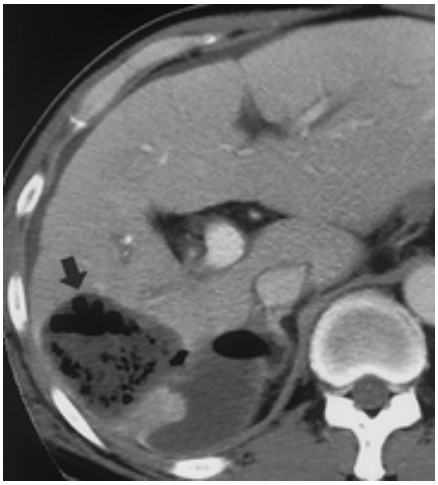
Bleeding is an important complication that can occur during and immediately after ablation. Complication can also depend on tumor location and the character of underlying parenchyma. Coagulation disorder in patients with end stage liver disease, patients with cirrhosis, higher vascularity of hepatocellular tumors compared to metastases are some factors that can contribute to bleeding complication. The bleeding may also develop from direct mechanical injury to the vessels by the RF needle rather than from thermal injury to the vessels. An arteriovenosus fistula or pseudoaneurysm can also develop from direct traumatic injury.
In order to minimize bleeding, screening for coagulopathy before procedure, placing of the RF needle electrode safely without transversing major vessels, cauterization of the needle tract after ablation and not to reposition needle many times can be preventive. Colour Doppler of the needle tract can also be helpful in early detection of arterial bleeding. Detection of important clinical signs and analysis of blood tests is essential for early detection of bleeding **[22].**

Emergency angiogram shows brisk arterial bleeding from hepatic artery **[21]**

Infection; **[21, 22]**

Sepsis and abscess can be seen after ablation procedure. Risk factors for hepatic abscess or sepsis are bacterial contamination of the hepatic parenchyma and biliary tract, bilioenteric anastomosis and bilioenteric fistula. Diabetic patients are at greater risk for infection because of their low immune system.

Diagnosis of abscess can sometimes be delayed because fever is not only symptom of abscess but it is also a symptom of postablation syndrome which is seen frequently after ablation. Therefore, if a fever lasts for over 2 weeks, the possibility of abscess formation should be considered. Prophylactic use of antibiotics may be helpful in patients with high risk of infection. New gas bubbles in ablated area not seen previously can be sign of abscess formation. Minimal amount of air can be seen immediately in CT scan after RF in ablated area and these should not be misdiagnosed as abscess. These minimal air bubbles usually resolve within 1 month. Most abscess can be treated with aspiration or percutaneous catheter drainage coupled with antibiotics.



One week follow up shows a gas forming abscess (arrow) in the ablated area with a perihepatic fluid **[22]**

Tumor seeding;

Tumor seeding usually occurs 3-12 months after RF ablation. Seeding of the needle track, pleura, or peritoneum can be seen depending on tumor location, and is more likely to occur with aggressive tumors in a subcapsular or superficial location. Poor differentiated tumor, hepatocellular carcinoma are risk factors for tumor seeding **[21, 23, 24, 25]**. Furthermore it is recommended to avoid treating an exo-phytic tumor percutaneously **[22].**

There can be different mechanism for tumor seeding. Tumor cells may adhere to biopsy needle or electrode during its withdrawal. With bleeding tumor cells may come into track.

Cells may be forced into the track by sudden intratumoral hyperpressure. Cells can also be driven in when saline is injected into the tumor. Other risk factor for seeding is preprocedural biopsies, poor differentiation of the tumor, no cauterization of the electrode track and a perpendicular approach to subcapsular tumors **[23].**

To avoid tumor seeding the number of punctures and the amount of repositioning of the RF needle should be minimize and a sufficient portion of normal hepatic parenchyma along the needle tract is required, especially in the case of subcapsular tumor **[22].** Sufficient RF energy to heat the tissue surrounding the electrode before it withdraws ("hot withdrawal") induces coagulation and this can reduce complications of tumour seeding and bleeding **[21, 24]**

Tumor seeding after RF ablation of a metastatic liver nodule **[21]**

Thermal damage to nontarget structures;

The heat from RF can also coagulate irreversibly and damage the organs adjacent to ablated tumor. Subcapsular location of the tumor can give raise to complications to adjacent organs. Radiofrequency is supposed to destroy the tumor with a safety margin of 0.5 -1 cm of healthy parenchyma. This leads to heating of structures that are located with in 0.5-1 cm from tumor margin **[26].** The gallbladder, bile ducts and bowl are sensitive to thermal energy. Bile duct strictures, cholecystitt and perforated bowl can be seen. Perforation of the gastrointestinal wall has been observed only when the target lesion is within 1 cm of the liver capsule or adjacent to a gastrointestinal lumen **[21].** Of the adjacent organs, the colon is most sensitive to heat because of its thin wall, and colon perforation is the most frequently reported complication involving adjacent organs **[26].** Gastric complications are rare because of the relatively thick wall of the stomach. Small bowl because of its mobility is protected as compared to fixed colon.

Ground pad burns;

The use of high current RF technique has increased the risk of burns at the ground pad site. A larger surface area of the return ground pad is required for more energy to be dispersed. Serious skin burns were reported during early experience when insufficiently sized ground pad were use. This complication has become relatively rare because large ground pads are used and guidelines to prevent burn are followed **[21, 22].**

Thoracic complications;

When tumor mass is located in the dome of the liver, pneumothorax and hemothorax can occur. If a patient has symptoms like dyspnoea or chest pain after ablation, chest radiograph or CT should be taken to exclude these complications. Diaphragmatic thermal injury is also possible when tumor is present in the dome of the liver. Diaphragmatic injury is self-limited with conservative treatment **[22].**

Postablation syndrome;

This is considered as a minor complication. It consists of a group of symptoms that are pain at the ablation site, shoulder pain, fever, nausea, vomiting, arthralgia, headache, tiredness, and loose stools. Post ablation occurs within a few days after ablation and persists for 2-8 weeks. This is often seen after ablation of large tumors (> 4-5 cm in diameter). Pain medication and rest is the treatment **[21].**

Risk factors for complications:

RF ablation of subcapsular tumours carries a higher risk of intraperitoneal bleeding, subcapsular haematoma, seeding and visceral damage. Ablation of central tumours predisposes to biliary tract and central vessel damage. Complications after RF of hepatocellular carcinoma are more common in child-Pugh class C than in class A or class B. In percutaneous approach thermal damage to neighbouring organs is seen exclusively. Tumor seeding is also seen often in percutaneous approach because the impossibility of coagulating the electrode track for superficial tumor. For large and multiple tumors where extensive procedures are used, there is a higher risk of liver failure, ground pad skin burn, myoglobenimea or myoglobinuria, thrombocytopenia and central hyperthermia **[23].** Complication rate increases also with increasing numbers of punctures, larger volumes of necrosis, more advanced Child Pugh class and treatment of lesions close to the diaphragm, into the liver hilum, close to vessels or viscera **[12].**

Different strategies for prevention from complications can be, not to perform ablation on patients with high risk of complications. Therefore coagulopathy, underlying hepatic reserve and tumor location to major structures, bile ducts, and intestine should be evaluated before treatment. Another method can be selection of the treatment procedure which gives proper visualization of tumor and adjacent structures. The open and laparoscopic approaches are better in isolating the lesion from adjacent structures and give better control of bleeding from the surface of the liver **[22].**

Rate of complications can also be lowered by avoiding Pringle maneuver during radiofrequency ablation in cirrhotic patients, caution when treating patients with bilioenteric anastomosis and who having a tumor less than 1 cm from adjacent organs, especially colon that is heat sensitive **[26].**

DISCUSSION

The most striking characteristics from the present literature study is that evidence for a beneficial effect of RFA is weak, and even the UK report from 2003 **[15]** seems to recommend RFA treatment despite lack of evidence. The report concludes: "RFA has the potential to cure some patients and can prolong survival in many others". But the literature basis for this report was one single prospective report with low quality and further three small patient series with very limited information. Even the UK report seems to recommend RFA in spite of very poor evidence base.

Without treatment the median survival of HCC is 4 to 20 months and for CRM the median survival is 5 to 13 months is reported from one center **[5].** In patients with metastatic disease confined to liver and without any treatment, another report gives median 9 months **[27]**. Those with solitary tumours and without any active treatment have a 3-year survival rate of 20% **[28]**.

In this paragraph I will describe the results from six selected articles. The best overall survival rates according to the results from the six articles included in the present study for RFA are 93% for 1-year **[29]**, 69% for 2-years **[29]**, and 63% for 3-years **[20]**. There is only one study that gives 4-years survival rate of 22% **[7]**. This survival rates compares favourably with the natural course of the disease, and the evidence for treatment benefits, mostly lacking in the UK report, now seems to increase. As the mean survival is concerned it is 36 months in one study **[14]** that varies a lot from another with 10 months as a mean survival rate **[19].** Two of the articles **[7, 11]** among these six, used combined RFA and resection as a treatment modality. Abdalla et al **[7]** gives 43% and 36% survival rates at 3 and 4-years. The other study **[11]** gives only result in the form of mean survival of 45.5 months. From these results one can see that 43% survival rate at 3-year with resection+RFA of CRM is lower than 50% in another study for CRM **[6]** where only RFA was used, but it is higher than 37% in the study **[7]** where RFA was used. Accordingly, it is difficult to give exact figures for survival after RFA as a treatment modality, as the variation is significant. Surgical resection of primary and metastatic liver tumor is the optimal treatment modality with curative effect, offering a 5-years survival rate between 20% and 35% **[30, 31].** The 3, 4, and 5-years survival rate after hepatic resection of colorectal metastases was 73%, 65%, and 58% respectively In Abdalla's report **[7].** According to a recent report from March 2006 **[32]** with a follow up period of 10

years, the overall survival after hepatic resection of colorectal metastases at 1, 5, and 10 years was 93%, 47%, and 28%, respectively. From these results of resection we can see that resection has higher overall survival than only RFA and resection+RFA. Local recurrence was 4.7% after a mean follow-up period of 14 months in lesions treated with laparoscopic RFA **[19]** versus 7.9% for HCC and 10.5% for metastases after follow-up 3-57 months, treated with percutaneous RFA **[20].** Local recurrence was seen in 9% of patients after only RFA, in 5% after RFA+resection and 2% after resection only in the same way intrahepatic recurrence was seen in 44% patients after RFA only, in 28% after RFA+resection and in 11% after resection only **[7].** According to these results local and intrahepatic recurrence is lowest after resection and it is lower in resection+RFA than in RFA only. Among these six studies the mortality rate differs from 3.4% **[29]** to 37% **[19]** after 7 months of ablations and after a mean follow up period of 14 months (range, 2-27 months) respectively**.** Additional new tumors were identified in 37% of patients by laparoscopic RFA that was not detected on preoperative imaging.

The overall survival at 1, 3 and 5-years was 71%, 21% and 14% in Gilliams report **[2].** This is the only study that gives a survival rate at 5 years, all other studies gives survival results mainly up to 3-years. This survival rate of 14% after RFA is much lower than survival rate of 58% at 5-years after resection **[7].** In White T et al study **[3]** survival rate at 1-year was 75% that correspond to 71% in Gilliams report, but still there is a wide range of difference in survival rate in all studies. Intrahepatic recurrence after a mean follow up of 14.6±9.2 months and 17 months was 53.9% in one study **[33]** and 50% in another **[2]** after the RFA treatment of mix tumor and CRM respectively. Again we can see that the intrhepatic recurrence of 50% is much higher than 11% after resection and 28% after RFA+resection **[7].**

Complications related to RFA procedure is divided in the most studies into major and minor complications. Major complications were defined as events that if left untreated could threaten patient's life, increase hospital stay and morbidity **[24, 26, 34].** Major complications ranged from 0.9% **[34]** to 19.8% **[11]**. and minor from 4.7% **[24]** to 32.5% **[25].** In some studies death is included in major complications while in other it is given separately. The most common complications were hepatic abscess, peritoneal haemorrhage, skin burn, perforation of gastrointestinal tract and biliary leakage. According to a review article of 3670 patients **[23]** the complication rate was 7.2%, 9.5, 9.9 and 31.8% after percutaneous, laparoscopic, simple open and combined open approaches respectively. The mortality rate

was 0.5%, 0%, 0% and 4.5% respectively **[23].** Two large studies **[22, 24]** give on the other hand percutaneous complication rate 2.4%. In another study **[19]** with laparoscopic RFA with 27 patients there was 1 case of postoperative bleeding**.** With combined RFA+resection complication rate was 19.8% including death **[11]**. Complication rates can varies a lot in all these studies. According to these results the complication rate is higher in resection +RFA than in only RFA treatment, and it can be because the RFA is a less invasive procedure. Mortality as a complication of RFA is summarized in the following table.

Study reference	**Mortality rate % (no. of patients)**	**Number of patients and complications**
23	0.5% (20)	7 (0.2%) Sepsis 7 (0.2%) liver failure 4 (0.1%) cardiac complications 1 (0.0%) peritoneal bleeding 1 (0.0%) bile duct stricture
22	0.09% (1)	Peritoneal bleeding
24	0.3% (6)	2 intestinal perforation 1 peritonitis 1 tumor rupture, massive haemorrhage 1 stenosis of right bile duct 1 sudden death of unknown cause
34	0.3% (1)	Liver decompansation
26	1.6% (5)	1 liver insufficiency 1 colon perfusion 3 portal vein thrombosis
11	2.3% (4)	2 liver failure 1 postoperative bleeding 1 cause not given

Complications as a cause of death and mortality rate in studied articles

Some factors can affect the outcome of results in different studies and these should be considered when analyse the results. The length of follow up can be different in different studies such that the results can be different in one study with very short follow up period as compare to other in which the follow up period can be comparatively longer. Inadequate length of studies can also affect results like local recurrence, intra or extra hepatic recurrence. Randomised controlled trials of radiofrequency ablation are lacking **[9].** Outcome following RFA can be difficult to interpret, since most studies report recurrence per lesion rather than per patient, and most studies report outcome for patients with mixed tumor type using different techniques of ablation with different equipment **[7]**. Inclusion criteria for patients can also be different. As mentioned above patients with unresectable are the main criteria for treatment of RFA, but other additional factors like chemotherapy as an adjuvant treatment can be inclusion criteria in some studies **[1, 3]** but it can be exclusion criteria in other **[19].** Technical development in RF treatment can give difference in results from newly published studies as compare to earlier studies.

All these results are from uncontrolled non-randomized studies, and there is lack of evidence based medicine to conclude that RFA is very efficient treatment method for liver tumors. To answer this question it is important with RCT and comparing of controlled group with interventional group. After search in Cochrane database it was only one review article **[16]** on two randomised clinical trials. One trial **[17]** including 102 patients, compared RFA versus percutaneous ethanol injection for small hepatocellular carcinoma. Another trial **[18]** compared RFA versus percutaneous microwave coagulation for 72 patients, but the results from these trials cannot be generalized because these trials compare two different treatment modalities. The only method to get results that can conclude about the treatment efficacy of RFA is to compare one control group without treatment or placebo with interventional group in which patients get RFA. But it is ethically not possible because patients with liver tumors can not be left untreated when results from the trials show that resection can be curative treatment for patients that have disease confined to liver and with good hepatic function, and that RFA may give long survival than if they left untreated. More randomised trials and evidence based medicine requires to evaluate the efficacy and safety of RFA.

Conclusion

Initial treatment with RFA in patients with unresectable hepatic liver tumours or poor liver function seems to be more effective compared to other local therapies. A review article **[9]** included one study **[35]** in which RFA and cryotherapy were compared. Procedure related complications were higher (41%) in cryotherapy as compared to 3% in RFA. Tumor recurrence was 2% in lesions treated with RFA, compared to 13% in those treated with cryotherapy. In another study **[36]** from the same review, RFA led to higher frequency of complete necrosis (90%) of tumors than with percutaneous ethanol injection (80%) but the complication rate was higher with ablation (2%) than with ethanol injection (0%).

Advances in chemotherapy are improving the survival in unresectable CRM. 5 fluourouracil (5-FU) and folinic acid (FA) remains the foundation of treatment and gives an improvement in median survival from 6 to 12 months. Two recently introduced drugs oxaliplatin and irenotecan, in combination with 5-FU-FA gives a median overall survival of 15-20 months. With the addition of bevacizumb the median survival appears now to exceed 20 months. Similar results can be obtained with hepatic arterial infusion of 5 –FU-FA although the toxicity is quite distinct from that seen in systemic administration of 5-FU **[28].** Chemotherapy can reduce tumor volume and patients with unresectable disease can undergo effective resection **[2].**

Hepatic resection is the only treatment of cure for patients with liver tumors who have disease confined to the liver. The operative mortality for major liver resection has reduced with development in the operative techniques and postoperative care, but mortality is still significant. According to review article **[4]** operative mortality ranged from 0% to 7% with haemorrhage, sepsis and liver failure as the causes of death, and the morbidity between 22-39%.Another recent report from 2006 **[32]** had a 5-years survival rate of 47% after a 10-years follow up period. Pawlik et al **[11]** and two review articles **[12, 4]** gives result from resection, RFA and combined RFA+resection and it seems that both mortality and morbidity is higher with resection as compare to other two modalities, and that RFA being the minimal invasive procedure has lowest rate of mortality and complications. As survival is concerned, resection gives higher overall survival than other modalities **[7].**

Radiofrequency ablation is just one of the options for patients with hepatic tumors. Selection of RFA should be made only after consideration of the alternative therapies option. Patients should be considering for hepatic resection if there are not contraindications. At present the radiofrequency ablation seems to be a promising therapy but this is based on uncontrolled trials, and as mentioned earlier even the UK report from 2003 **[15]** seems to recommend RFA treatment despite lack of evidence and the literature prospective report with low quality and patient series with very limited information. The evidence based knowledge about the radiofrequency ablation for the treatment of hepatic tumors is lacking. Randomised trials are not available to support use of this technique. After search in Cochrane database only one review was present and this too compared different treatment modalities, and trials with a control group was lacking. But it is ethically not possible to perform randomised trials with control group giving placebo or no treatment; because patients with hepatic tumors can not be left untreated when studies conclude that there are treatment options for such patients. Therefore conclusive evidence on survival benefit from treatment of RFA is awaited.

REFERENCES

1 Solbiati L, Liraghi T, Goldberg SM et al. Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long term results in 117 patients. *Radiology 2001; 221: 159-166*

2 Gilliams AR, Lee WR. Radio-frequency ablation of colorectal liver metastses in 167 patients. *Eur Radiol (2004) 14:2261-2267*

3 White TJ, Roy-choudhry SH, Breen DJ et al. Percutaneous radiofrequency ablation of colorectal hepatic metastases-initial experiences. *Dig Surg 2004; 21: 314-320*

4 Liu LX, Zhang WH et al. (Review) Current treatment for liver metastases from colorectal cancer. *World J Gastroenterol 2003; 9(2): 193-200*

5 McMurrick P, Nelson H (1997). Liver-directed therapies for gastrointestinal malignancies. *Current Opin Oncol 9: 367-372*

6 Lannitti DA, Dupuy DE, Mayo-Smith WW et al. Hepatic radiofrequency ablation. *Arch Surg. 2002; 137: 422-427*

7 Abdalla EK,Vauthey JN,Ellis LM et al. Recurrence and outcomes following hepatic resection,radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg 2004;239: 818-827*

8 Baere T, Elias D, Dromain C et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. *AJR 2000; 175: 1619-1625*

9 Decadt B, Siriwardena A. Radiofrequency ablation of liver tumours: systematic review. *Lancet Oncol 2004; 5: 550-60*

10 Lencioni R, Crocetti L, Cioni D et al. Percutaneous radiofrequency ablation of hepatic colorectal metastases. *Invest Radiol 2004; 39: 689-697.*

11 Pawlik TM,Izzo F, Choen DS. et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. *Ann Surg Oncol, 2003 Nov;10(9):1059-69.*

12 Gillams A R. Review article Liver ablation therapy. *The British Journal Of Radiology 2004; 77: 713-727*

13 Curley SA, Izzo F. Laparoscopic radiofrequency. *Annals of surgical oncology 2000; 7(2): 78-79.*

14 Solbiati L, Liraghi T, Goldberg SM et al. Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long term results in 117 patients. *Radiology 2001; 221: 159-166*

15 WEB-paper September 2003: Interventional procedure overview of radiofrequency ablation for the treatment of colorectal metastases, *National Institute for Clinical Excellence*

16 Galandi D, Antes G. Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma. *The Cochrane database of systematic reviews 2004, issue 2.* Art. No: CD003046.pub2. DOI: 10. 1002/14651858.CD003046.pub2.

17 Lencioni R, Allgaier HP, Cioni D et al. Small hepatocellular carcinoma: randomised comparioson of radio-frequency thermal ablation and percutaneous ethanol injection. *Radiology 2003; 228: 235-40.*

18 Shibata T, Limuro Y, Yamamoto Y et al. Small hepatocellular carcinoma: comparison of radio-frequency and percutaneous microwave coagulation therapy. *Radiology 2002; 223: 331-7.*

19 Chung MH, Wood TF, Tsioulias GJ et al. Laprascopic radiofrequency ablation of unresectable hepatic malignancies. *Surg Endosc 2001; 15: 1020-1026*

20 Chen MH, Yang W, Yan K. Treatment efficacy of radiofrequency ablation of 338 patients with hepatic malignant tumor and the relevant complications. *World J Gastroenterol 2005; 11(40): 6395-6401*

21 Rhim H, Gerald D, Chintapalli K et al: Radiofrequency thermal ablation of abdominal tumors; lessons learned from complications. *RadioGraphics 2004; 24: 41-52*

22 Rhim H, Yoon K, Lee J et al: Major complications after radio-frequency thermal ablation of hepatic tumors; spectrum of imaging findings. *Radiographics 2003; 23: 123-136*

23 Mulier S, Mulier P, Ni Y et al: Complications of radiofrequency coagulation of liver tumors. *British Journal Of Surgery 2002; 89: 1206-1222*

24 Livraghi T, Solbiati L, Meloni M et al: Treatment of focal liver tumors with percutaneous radio-frequency ablation; complications encountered in a multicenter study. *Radiology 2003; 226: 441-451*

25 Buscarini E, Buscarini L. Radiofrequency thermal ablation with expandable needle of focal liver malignancies; complication report. *Eur Radiol 2004; 14: 31-37*

26 Baere T, Risse O, Kuoch V et al: Adverse events during radiofrequency treatment of 582 hepatic tumors. *AJR 2003; 181: 695-700*

27 Stangl R, Atendorf-Hofman A, Charnley RM. Factors influencing the natural history of colorectal liver metastases. *Lancet 1994; 343: 1405-10*

28 Bruce R. Bacon, John G. O`Grady Adrian M. Di Bisceglie: *Clinical Hepatology*. ISBN 0-323-03675-9. Second edition.

29 Solbiati L, Goldber N, Lerace T et al. Hepatic metastases: percutaneous radiofrequency ablation with cooled tip electrode. *Radiology 1997; 205: 367-373*

30 Fong Y, Cohen AM, Fortner JG et al. Liver resection for colorectal metastases. *J Clin Oncol 1997; 15: 938-46.*

31 Tuttle TM. Hepatectomy of noncolorectal liver metastases. In: Curley SA, ed. Liver cancer. New York: Springer-Verlag Publishers; 1998: 201-11

32 Wei AC, Greig PD, Grant D et al. Survival After Hepatic Resection for Colorectal Metastases: A 10-Year Experience. *Ann Surg Oncol. 2006 Mar 10; [Epub ahead of print].* ISSN: 1068-9265 (Paper) 1534-4681 (Online) DOI: 10.1245/ASO.2006.05.039

33 Tepel J, Hinz S, Klomp HJ et al. Intraoperative radiofrequency ablation (RFA) for irresectable liver malignancies. *EJSO (2004) 30; 551-555*

34 Giorgio A, Tarantino L, Stefano G et al. Complications after percutaneous saline-enhanced radiofrequency ablation of liver tumors: 3 year experience with 336 patients at a single senter. *AJR 2005; 184: 207-211*

35 Pearson AS, Izzo F, Fleming RY et al. Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. *Am J Surg 1999; 178: 592-99.*

36 Livraghi T, Goldberg SN, Lazzaroni S et al. Small hepatocellular carcinoma: treatment with radiofrequency-ablation versus ethanol injection. *Radiology 1999; 210: 655-61.*